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TOPICAL HAZARD EVALUATION PROGRAM OF CANDIDATE INSECT
REPELLENTS A13-3822 (U) ARMY ENVIRONMENTAL HYGIENE
AGENCY ABERDEEN PROVING GROUND MD J V WADE ET AL.
25 JAN 84 USAEHA-75-51-0334-84

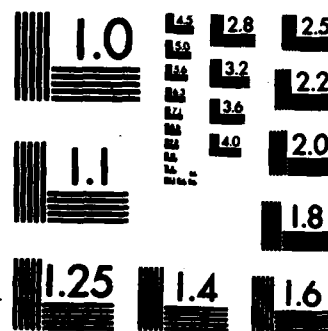
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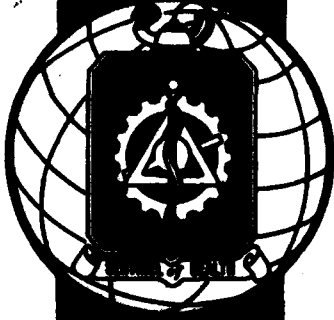




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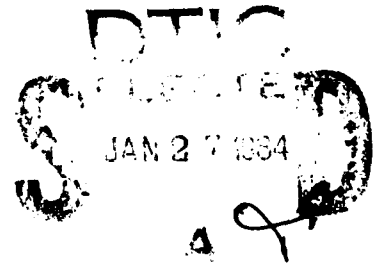
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**UNITED STATES ARMY
ENVIRONMENTAL HYGIENE
AGENCY**

ABERDEEN PROVING GROUND, MD 21010

TOPICAL HAZARD EVALUATION PROGRAM
OF
CANDIDATE INSECT REPELLENTS AI3-38225a, AI3-38192a,
AI3-38194a, AI3-38599a, and AI3-38427a
US DEPARTMENT OF AGRICULTURE PROPRIETARY CHEMICALS
STUDY NUMBERS 75-51-0334-84, 75-51-0336-84,
75-51-0344-84, 75-51-0355-84, and 75-51-0356-84
JUNE 1981 - NOVEMBER 1983



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REPORT DOCUMENTATION PAGE		READ INSTRUCTIONS BEFORE COMPLETING FORM
1. REPORT NUMBER 75-51-0334-84	2. GOVT ACCESSION NO.	3. RECIPIENT'S CATALOG NUMBER
4. TITLE (and Subtitle) Topical Hazard Evaluation Program of Candidate Insect Repellents AI3-38225a, AI3-38192a, AI3-38194a, AI3-38599a, and AI3-38427a, US Department of Agriculture Proprietary Chemicals, Study No. 75-51-0334-84, 75-51-0336-84, 75-51-0344-84, 75-51-0355-84, and 75-51-0356-84, Jun 81 - Nov 83		5. TYPE OF REPORT & PERIOD COVERED Final, Jun 81 - Nov 83
7. AUTHOR(s) John V. Wade, DVM, CPT(P), VC John G. Harvey, Jr.		6. PERFORMING ORG. REPORT NUMBER
9. PERFORMING ORGANIZATION NAME AND ADDRESS Commander US Army Environmental Hygiene Agency Aberdeen Proving Ground, MD 21010		8. CONTRACT OR GRANT NUMBER(s)
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18. SUPPLEMENTARY NOTES		
19. KEY WORDS (Continue on reverse side if necessary and identify by block number) <div style="display: flex; justify-content: space-between;"> <div> USDA Proprietary Chemicals AI3-38225a AI3-38192a AI3-38194a AI3-38599a </div> <div> AI3-38427a Topical Hazard Evaluation Program Skin Irritation Eye Irritation Photochemical Irritation </div> <div> ALD Guinea Pig Sensitization </div> </div>		
20. ABSTRACT (Continue on reverse side if necessary and identify by block number) Chemicals AI3-38192a, AI3-38599a, and AI3-38427a produced no primary skin irritation. Chemicals AI3-38225a and AI3-38194a produced mild irritation of the intact skin and the skin surrounding an abrasion. Chemical AI3-38599a was noninjurious to the eyes of rabbits. Chemical AI3-38192a produced mild injury to the cornea; chemicals AI3-38225a, AI3-38427a, and AI3-38194a produced mild injury to the cornea and, in addition, some injury to the conjunctiva upon application to the eyes of rabbits. Chemicals AI3-38225a, AI3-38192a, AI3-38599a, and AI3-38427a did not produce a sensitization reaction. Chemical		

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20. ↗ AI3-383194a produced a slight sensitization reaction in 6 of the 10 guinea pigs tested. All chemicals were relatively nontoxic by ingestion and did not potentiate photoirritation. Recommend that chemicals AI3-38225a, AI3-38192a, AI3-38599a, and AI3-38427a be approved for further testing as candidate insect repellants. Recommend that chemical AI3-38194a be disapproved for further testing due to its sensitizing potential. ↗

Unclassified

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DEPARTMENT OF THE ARMY CPT(P) Wade/slw/AUTOVON
U. S. ARMY ENVIRONMENTAL HYGIENE AGENCY 584-3980
ABERDEEN PROVING GROUND, MARYLAND 21010

REPLY TO
ATTENTION OF
HSHB-OT/MP

25 JAN 1984

SUBJECT: Topical Hazard Evaluation Program of Candidate Insect Repellents
AI3-38225a, AI3-38192a, AI3-38194a, AI3-38599a, and AI3-38427a,
US Department of Agriculture Proprietary Chemicals, Study Numbers
75-51-0334-84, 75-51-0336-84, 75-51-0344-84, 75-51-0355-84, and
75-51-0356-84, June 1981 - November 1983

Executive Secretary
Armed Forces Pest Management Board
Forest Glen Section, WRAMC
Washington, DC 20307

EXECUTIVE SUMMARY

The purpose, essential findings, and major recommendations of the inclosed report follow:

a. Purpose. The purpose of this program is to provide guidance for entomological testing of the candidate insect repellents AI3-38225a, AI3-38192a, AI3-38194a, AI3-38599a, and AI3-38427a, by means of laboratory animal studies using New Zealand White rabbits, Sprague-Dawley rats, and albino Hartley guinea pigs.

b. Essential Findings. Chemicals AI3-38192a, AI3-38599a, and AI3-38427a produced no primary skin irritation. Chemicals AI3-38225a and AI3-38194a produced mild irritation of the intact skin and the skin surrounding an abrasion. Chemical AI3-38599a was noninjurious to the eyes of rabbits. Chemical AI3-38192a produced mild injury to the cornea; chemicals AI3-38225a, AI3-38427a, and AI3-38194a produced mild injury to the cornea and, in addition, some injury to the conjunctiva upon application to the eyes of rabbits. Chemicals AI3-38225a, AI3-38192a, AI3-38599a, and AI3-38427a did not produce a sensitization reaction. Chemical AI3-383194a produced a slight sensitization reaction in 6 of the 10 guinea pigs tested. All chemicals were relatively nontoxic by ingestion and did not potentiate photoirritation.

c. Major Recommendations. Recommend that chemicals AI3-38225a, AI3-38192a, AI3-38599a, and AI3-38427a be approved for further testing as candidate insect repellants. Recommend that chemical AI3-38194a be disapproved for further testing due to its sensitizing potential.

FOR THE COMMANDER:

1 Incl
as (5 cy)

John C. Gaydos
JOEL C. GAYDOS, M.D.
Colonel, MC
Director, Occupational and
Environmental Health

CF:
HQDA (DASG-PSP) w/o Incl
Cdr, HSC, (HSPA-P)
Comdt, AMS (HSHA-P)
Dir, Advisory Cen on TOX, NRC (2 cy)
USDA, ARS (Dr. Terrence McGovern)
USDA, ARS-Southern Region (3 cy)
Cdr, USAHBRDL [SGRD-OPM/LTC(P) Reinert]

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DEPARTMENT OF THE ARMY
U. S. ARMY ENVIRONMENTAL HYGIENE AGENCY
ABERDEEN PROVING GROUND, MARYLAND 21010

REPLY TO
ATTENTION OF
HSHB-OT/MP

TOPICAL HAZARD EVALUATION PROGRAM
OF
CANDIDATE INSECT REPELLENTS AI3-38225a, AI3-38192a,
AI3-38194a, AI3-38599a, and AI3-38427a
US DEPARTMENT OF AGRICULTURE PROPRIETARY CHEMICALS
STUDY NUMBERS 75-51-0334-84, 75-51-0336-84, 75-51-0344-84,
75-51-0355-84 and 75-51-0356-84
JUNE 1981 - NOVEMBER 1983

1. AUTHORITY.

a. Letter, US Department of Agriculture - Agricultural Research, Southern Region, Insects Affecting Man and Animals Research Laboratory, Gainesville, Florida, 18 June 1981.

b. Letter, US Department of Agriculture - Agricultural Research, Southern Region, Insects Affecting Man and Animals Research Laboratory, Gainesville, Florida, 26 February 1982.

c. Letter, US Department of Agriculture - Agricultural Research, Southern Region, Insects Affecting Man and Animals Research Laboratory, Gainesville, Florida, 3 September 1981.

d. Memorandum of Understanding between the US Army Environmental Hygiene Agency; the US Army Health Services Command; the Department of the Army, Office of The Surgeon General; the Armed Forces Pest Control Board; and the Department of Agriculture, Agricultural Research, Science and Education Administrations; titled Coordination of Biological and Toxicological Testing of Pesticides, effective 23 January 1979.

2. REFERENCE. Toxicology Division Topical Hazard Evaluation Program Procedural Guide, US Army Environmental Hygiene Agency (USAEHA), January 1982.

3. PURPOSE. The purpose of this program is to provide guidance for further entomological testing of the candidate insect repellents AI3-38225a, AI3-38192a, AI3-38599a, AI3-38427a, and AI3-38194a, US Department of Agriculture (USDA) Proprietary Chemicals.

4. SUMMARY OF FINDINGS. Hazard evaluations of the candidate insect repellants AI3-38225a, AI3-38192a, AI3-38599a, AI3-38427a, and AI3-38194a, USDA Proprietary chemicals, were conducted by this Agency using New Zealand White rabbits, Sprague-Dawley rats and albino Hartley guinea pigs. A tabular presentation of animal toxicity data developed by this Agency follows:†

* In conducting the studies described in this report, the investigators adhered to the "Guide for the Care and Use of Laboratory Animals," US Department of Health, Education, and Welfare Publication No. (NIH) 80-23, revised 1978.

† The studies reported herein were performed in animal facilities fully accredited by the American Association for the Accreditation of Laboratory Animal Care.

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Study Nos. 75-51-0334-84, 75-51-0336-84, 75-51-0344-84, 75-51-0355-84, and 75-51-0356-84, Jun 81 - Nov 83

TABLE. PRESENTATION OF DATA

TEST	RESULTS	INTERPRETATION
SKIN IRRITATION STUDIES		
Rabbits		
Single 24-hour application to intact and abraded skin of New Zealand White rabbits.	Chemicals AI3-38192a, AI3-38599a, and AI3-38427a did not produce irritation of the intact skin or of the skin surrounding an abrasion.	USAEHA Category I (ref Appendix A)
0.5 mL technical grade chemical applied to each of six rabbits.	Chemicals AI3-38225a and AI3-38194a produced mild primary irritation of the intact skin and of the skin surrounding an abrasion.	USAEHA Category II (ref Appendix A)
EYE IRRITATION STUDIES		
Rabbits		
Single 24-hour application of 0.1 mL technical grade chemical to one eye of each of nine New Zealand White rabbits. Three of the nine rabbits had the eye flushed with warm water for 1 minute, 25 seconds after application.	Chemical AI3-38599a was noninjurious to the eye.	USAEHA Category A (ref Appendix A)
	Chemical AI3-38192a produced mild injury to the cornea.	USAEHA Category B (ref Appendix A)
	Chemicals AI3-38225a, AI3-38427a and AI3-38194a produced mild injury to the cornea and, in addition, some injury to the conjunctiva.	USAEHA Category C (ref Appendix A)
	Washing with warm water decreased the ocular injury noted on application of chemicals AI3-38225a and AI3-38194a.	

Study Nos. 75-51-0334-84, 75-51-0336-84, 75-51-0344-84, 75-51-0355-84, and 75-51-0356-84, Jun 81 - Nov 83

TEST	RESULTS	INTERPRETATION
APPROXIMATE LETHAL DOSE		
Oral		
Rats (male) - no diluent	AI3-38225a 2871 mg/kg AI3-38192a >2871 mg/kg AI3-38194a >6761 mg/kg	These chemicals are relatively nontoxic by ingestion.
Rats (female) - no diluent	AI3-38599a >3333 mg/kg AI3-38427 >5000 mg/kg	

PHOTOCHEMICAL SKIN IRRITATION STUDIES

Rabbits

A single 0.05 mL application of a 25% (w/v) solution of each chemical and of a 10% (w/v) Oil of Bergamot solution (positive control) in 95% ethyl alcohol was applied to the intact skin of six rabbits. Five minutes after application, the rabbits were exposed to ultraviolet (UV) light (365 nm) for 30 minutes at a distance of 10-15 cm.

These chemicals did not produce photochemical irritation under test conditions.

These chemicals did not produce photochemical irritation under test conditions and are not expected to produce photoirritation in humans.

Control

Following UV exposure of the rabbits, 0.05 mL of test chemicals, positive control and diluent were applied to additional skin areas to serve as unirradiated control sites. Application areas were checked for skin irritation at 24, 48, and 72 hours.

Positive control application and irradiation caused greater irritant effects than in unirradiated skin areas.

Study Nos. 75-51-0334-84, 75-51-0336-84, 75-51-0344-84, 75-51-0355-84, and 75-51-0356-84, Jun 81 - Nov 83

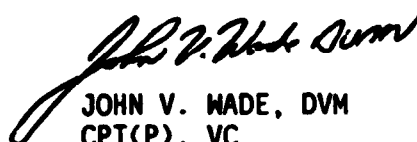
TEST	RESULTS	INTERPRETATION
SENSITIZATION STUDIES		
Guinea Pigs (Male)		
Intradermal (ID) injections of 0.1 mL of a 0.1% (w/v) solution of each tested chemical or of dinitrochlorobenzene (DNCB)* in a mixture containing 1 volume of propylene glycol and 29 volumes of saline:		
Ten test guinea pigs for each chemical were given 10 sensitizing doses over a 3-week period. After a 2-week rest, they were challenged with ID injections of each test compound.	Challenge doses of AI3-38225a, AI3-38192a, AI3-38599a, and AI3-38427a did not produce sensitization reactions. Chemical AI3-38194a produced slight sensitization reactions in 6 of 10 guinea pigs tested.	These chemicals are not expected to produce a sensitization reaction in humans. This chemical could produce a sensitization reaction in humans.
Control		
Ten positive control guinea pigs were sensitized over 3-weeks with DNCB. After a 2-week rest, they were challenged with ID injections of DNCB.	Challenge dose of DNCB in positive control guinea pigs produced a marked sensitization reaction in 10 out of 10 guinea pigs.	DNCB produced a marked sensitization reaction, indicating that these guinea pigs respond to sensitizing agents.

* A known skin sensitizer.

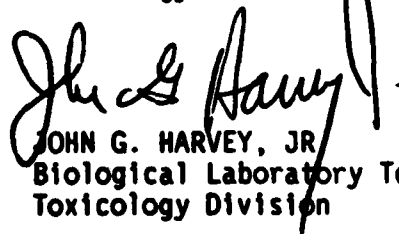
Study Nos. 75-51-0334-84, 75-51-0336-84, 75-51-0344-84, 75-51-0355-84, and 75-51-0356-84, Jun 81 - Nov 83

5. **CONCLUSION.** Chemicals AI3-38192a, AI3-38599a, and AI3-38427a produced no primary irritation. Chemicals AI3-38225a and AI3-38194a produced mild primary irritation of the intact skin and of the skin surrounding an abrasion. Chemical AI3-38599a was noninjurious to the eyes of rabbits. Chemical AI3-38192a produced mild injury to the cornea; chemicals AI3-38225a, AI3-38427a, and AI3-38194a produced mild injury to the cornea and, in addition, some injury to the conjunctiva upon application to the eyes of rabbits. Chemicals AI3-38225a, AI3-38192a, AI3-38599a, and AI3-38427a did not produce a sensitization reaction. Chemical AI3-38194a produced a slight sensitization reaction in 6 of the 10 guineas pigs tested. All chemicals were relatively nontoxic by ingestion and did not potentiate photoirritation. These studies were monitored by Analytical Quality Assurance Office (see Appendix B).

6. **RECOMMENDATION.** Recommend that chemicals AI3-38225a, AI3-38192a, AI3-38599a, and AI3-38427a be approved for further testing as candidate insect repellents. Recommend that chemical AI3-38194a be disapproved for further testing due to its sensitizing potential.


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APPROVED:


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Study Nos. 75-51-0334-84, 75-51-0336-84, 75-51-0344-84, 75-51-0355-84, and 75-51-0356-84, Jun 81 - Nov 83

APPENDIX A

TOPICAL HAZARD EVALUATION PROGRAM DEFINITIONS OF CATEGORIES OF COMPOUNDS BEING CONSIDERED FOR ACUTE SKIN APPLICATION

CATEGORY I - Compounds producing no primary irritation of the intact skin or no greater than mild primary irritation of the skin surrounding an abrasion. (INTERPRETATION: No restriction for acute application to the human skin.)

CATEGORY II - Compounds producing mild primary irritation of the intact skin and the skin surrounding an abrasion. (INTERPRETATION: Should be used only on human skin found by examination to have no abrasions or may be used as a clothing impregnant.)

CATEGORY III - Compounds producing moderate primary irritation of the intact skin and the skin surrounding an abrasion. (INTERPRETATION: Should not be used directly on the skin without a prophetic patch test having been conducted on humans to determine irritation potential to human skin. May be used without patch testing, with extreme caution, as clothing impregnants. Compound should be resubmitted in the form and at the intended use concentration so that its irritation potential can be reexamined using other test techniques on animals.)

CATEGORY IV - Compounds producing moderate to severe primary irritation of the intact skin and of the skin surrounding an abrasion and, in addition, producing necrosis, vesiculation, and/or eschars. (INTERPRETATION: Should be resubmitted for testing in the form and at the intended use concentration. Upon resubmission, its irritation potential will be reexamined using other test techniques on animals, prior to possible prophetic patch testing in humans, at concentrations which have been shown not to produce primary irritation in animals.)

CATEGORY V - Compounds impossible to classify because of staining of the skin or other masking effects owing to physical properties of the compound. (INTERPRETATION: Not suitable for use on humans.)

EYE CATEGORIES:

A. Compounds noninjurious to the eye. INTERPRETATION: Irritation of human eyes is not expected if the compound should accidentally get into the eyes, provided it is washed out as soon as possible.

B. Compounds producing mild injury to the cornea. INTERPRETATION: Should be used with caution around the eyes.

C. Compounds producing mild injury to the cornea, and in addition some injury to the conjunctiva. INTERPRETATION: Should be used with caution around the eyes and mucosa.

D. Compounds producing moderate injury to the cornea. INTERPRETATION: Should be used with extreme caution around the eyes.

E. Compounds producing moderate injury to the cornea, and in addition producing some injury to the conjunctiva. INTERPRETATION: Should be used with extreme caution around the eyes and mucosa.

F. Compounds producing severe injury to the cornea and to the conjunctiva. INTERPRETATION: Should be used with extreme caution. It is recommended that use be restricted to areas other than the face.

Study Nos. 75-51-0334-84, 75-51-0336-84, 75-51-0344-84, 75-51-0355-84, and 75-51-0356-84, Jan 81 - Nov 83

APPENDIX B

ANALYTICAL QUALITY ASSURANCE

The Analytical Quality Assurance Office certifies the following with regard to this study:

a. This study was conducted in accordance with:

(1) Standing Operating Procedures developed by the Toxicology Division, USAEHA.

(2) Title 21, Code of Federal Regulations, 1981 rev, Part 58, Good Laboratory Practice for Nonclinical Laboratory Studies.

b. Facilities were inspected during its operational phase to insure compliance with paragraph a above.

c. The information presented in this report accurately reflects the raw data generated during the course of conducting the study.



PAUL V. SNEERINGER, Ph.D.
Chief, Analytical Quality
Assurance Office

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